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Impact of the first-generation drug-eluting stent implantation on periprocedural myocardial injury in patients with stable angina pectoris

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ABSTRACT

Background and purpose: Percutaneous coronary intervention (PCI) with a drug-eluting stent (DES) is one of the standard treatments for patients with stable angina pectoris (AP). In spite of a notable effect in preventing restenosis after PCI, DES cannot improve the mortality of patients compared to a bare-metal stent (BMS). On the other hand, periprocedural myocardial injury (PMI) is related to poor prognosis in patients undergoing PCI. We compared DES to BMS in the incidence of PMI in patients with stable AP.
Methods and subjects: We enrolled 265 consecutive patients with AP undergoing successful stent implantation. A blood sample was obtained from all patients immediately before and 24 h after PCI. PMI was defined as an increase in creatine kinase-myocardial band isozyme fraction (CK-MB) greater than the upper limit of reference range 24 h after PCI. During the study period, sirolimus- and paclitaxel-eluting stents were used as DES. The strategy of PCI including the type of stent to implant was left to the discretion of the operator.
Results: Patients were divided into two groups (DES group, $n = 136$ and BMS group, $n = 129$). The incidence of PMI was significantly higher in the DES group than in the BMS group (24% vs. 12%, $p = 0.015$). Use of DES remained an independent predictor of PMI on multivariate logistic regression analysis after adjustment for confounding factors (odds ratio 2.20, 95% CI, 1.07–4.51, $p = 0.032$).
Conclusions: Implantation of the first-generation DES including sirolimus- and paclitaxel-eluting stents was associated with a higher incidence of PMI in patients with AP compared to BMS.

Introduction

Percutaneous coronary intervention (PCI) in patients with angina pectoris (AP) is a well-established treatment. However, restenosis after PCI remains a clinical limitation, because it attenuates the quality of life and may even increase the mortality of patients [1,2]. In such situations, drug-eluting stents (DESs) have dramatically suppressed neointimal hyperplasia and eventually reduced the risk of restenosis and the necessity of repeat revascularization after PCI compared to the bare-metal stent (BMS) [3–5]. Thus, DESs have been widely used in PCI. Unfortunately, the use of DES is reportedly equivalent to BMS in terms of long-term survival [6–8].

On the other hand, procedural-related complications such as flow-limiting dissection, branch occlusion, thrombus formation, no-reflow, and macroscopic embolization resulting in myocardial damage also remain clinical problems in PCI. Moreover, periprocedural myocardial injury (PMI) detected even after apparently non-complicated procedures is associated with future cardiovascular events [9–12]. Until now, there have been limited reports on whether or not DES use is related to a higher incidence of PMI. Thus, the aim of this study was to compare implantation of DES to that of BMS in the incidence of PMI in patients with stable AP.

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Table 1
Patient characteristics.

	All $n=265$	DES $n=136$	BMS $n=129$	p
Age (y)	68 ± 10	67 ± 10	69 ± 10	0.063
Male	213 (80)	110 (81)	103 (80)	0.878
Body mass index (kg/m^2)	23.7 ± 3.7	24.3 ± 3.6	23.1 ± 3.8	0.012
Clinical history				
Hypertension	201 (76)	106 (78)	95 (74)	0.439
Diabetes	131 (49)	75 (55)	56 (43)	0.065
Current smoker	73 (28)	32 (24)	41 (32)	0.086
Previous myocardial infarction	60 (23)	36 (26)	24 (19)	0.083
Multiple vessel disease	98 (37)	66 (49)	32 (25)	<0.001
Familial history of coronary heart disease	43 (16)	23 (17)	20 (16)	0.868
CK-MB before procedure (IU/l)	12.7 ± 6.7	13.3 ± 6.6	12.2 ± 6.7	0.168
CK-MB 24 h after procedure (IU/l)	18.2 ± 22.9	21.0 ± 23.6	15.4 ± 21.8	0.045
Total cholesterol (mg/dl)	176.7 ± 35.0	174.2 ± 33.4	179.4 ± 36.6	0.225
LDL-C (mg/dl)	103.2 ± 31.1	99.0 ± 27.6	107.7 ± 34.0	0.023
HDL-C (mg/dl)	46.1 ± 12.9	46.6 ± 12.1	45.5 ± 13.6	0.488
Triglyceride (mg/dl)	139.1 ± 72.6	141.2 ± 76.1	136.9 ± 69.0	0.630
Hemoglobin A1c (%)	6.2 ± 1.0	6.1 ± 1.0	6.2 ± 1.0	0.711
High-sensitivity C-reactive protein (mg/l)	4.8 ± 12.0	3.6 ± 10.4	6.2 ± 13.4	0.076
Left ventricular ejection fraction[a] (%)	61 ± 12	61 ± 13	62 ± 11	0.541
Medication				
Aspirin	265 (100)	136 (100)	129 (100)	
Thienopyridine drug	265 (100)	136 (100)	129 (100)	
ACE-I and/or ARB	154 (58)	88 (65)	66 (51)	0.017
Calcium channel blockers	117 (44)	65 (48)	52 (40)	0.265
Beta-blockers	72 (27)	40 (29)	32 (25)	0.411
Nitrates	53 (20)	31 (23)	22 (17)	0.283
Statins	265 (100)	136 (100)	129 (100)	
Insulin	19 (7)	12 (9)	7 (5)	0.345
Oral diabetes medications	77 (29)	44 (32)	33 (26)	0.110

Values are mean ± SD or number (%). DES, drug-eluting stent; BMS, bare-metal stent; CK-MB, creatine kinase-myocardial band isozyme fraction; PMI, periprocedural myocardial injury; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

[a] Left ventricular ejection fraction was measured by echocardiography.

Materials and methods

Study population

We enrolled a total of 265 consecutive stable AP patients with documented ischemia between September 2008 and April 2010 at Nagoya University Hospital. The inclusion criteria of the study were patients undergoing elective PCI with angiographically successful stent implantation for de novo coronary artery lesions except those located at left main trunk. Procedural success was defined as a final angiographic residual stenosis of <30% by quantitative coronary angiography (QCA) without flow-limiting dissection or occlusion of the large branch (>1 mm) or no-flow/slow-reflow phenomenon during a procedure, and a resulting Thrombolysis in Myocardial Infarction (TIMI) grade of 3 [13]. Exclusion criteria consisted of patients with chronic total occlusion, angioplasty with atherectomy, abnormal creatine kinase-myocardial band isozyme fraction (CK-MB) value prior to PCI, and/or contraindication to aspirin, thienopyridine, or statin treatment. The study protocol and chart reviews were approved by the institutional ethics committee. Written informed consent was given by all patients prior to procedures.

Quantitative coronary angiography and PCI procedure

All patients received treatment with oral aspirin (100 mg/day) and thienopyridine drug, and any statins at least two weeks prior to PCI. Heparin (10,000 IU) was administered intravenously immediately prior to the procedure. Coronary angiograms for QCA were obtained immediately prior to PCI, following an intracoronary infusion of 2.5 mg isosorbide dinitrate. The projection showing the maximal degree of stenosis (worst view) was selected for QCA. Analysis of QCA was performed using a contour detection minimum cost algorithm (QCA-CMS Version 3.0, MEDIS, Leiden, Netherlands). Lesion types were divided according to the American Heart Association/American College of Cardiology classification, and a complex lesion was defined as lesion type B2 or C [14]. PCIs were performed through the femoral or radial artery according to the standard techniques by experienced cardiologists. The strategy of PCI including type of stent to implant was left to the discretion of the operator. In our institution, a sirolimus- or paclitaxel-eluting stent (Cypher, Cordis Corp., Johnson & Johnson, Warren, NJ, USA and TAXUS, Express2 or Liberte; Boston Scientific, Natick, MA, USA, respectively) were adopted as DES during the study period. Platelet glycoprotein IIb/IIIa receptor inhibitors were not used because they were not available in Japan.

Evaluation of plasma markers

A blood sample was obtained from the atrial sheath just before and from the peripheral vein 24 h after PCI. CK-MB was measured using a commercially available immunoinhibition assay kit. The upper reference limit for CK-MB was 25 IU/l which represented the 99th percentile of values for reference control groups. PMI was defined as an increase in CK-MB greater than the upper limit of the reference range (ULN) 24 h after PCI, as previously described [15,16]. The data of various lipid, glucose, and inflammatory profiles were also measured immediately before PCI.

Statistical analysis

PASW ver. 18 (SPSS, Chicago, IL, USA) was used for all statistical analyses. Continuous variables were presented as mean ± standard deviations, and differences between the two groups were evaluated by the Student unpaired t-test or the Mann–Whitney U-test

Table 2
The incidence of periprocedural myocardial injury.

	All $n=265$	DES $n=136$	BMS $n=129$	p
CK-MB > 3× ULN	4 (2)	3 (2)	1 (1)	0.623
CK-MB > 5× ULN	0	0	0	–

Values are numbers (%). DES, drug-eluting stent; BMS, bare-metal stent; CK-MB, creatine kinase-myocardial band isozyme fraction; ULN, upper limit of the reference range.

if their distribution was abnormal. Categorical variables were presented as numbers (percentages), and comparisons across the two groups were performed by the chi-square test or Fisher exact test. We performed univariate logistic regression analyses to evaluate the relationship between PMI and other confounders. And then, multivariate logistic regression analysis was conducted to adjust for these variables with p-value <0.2 at univariate logistic regression analysis and multiple vessel disease, lesion length, and reference vessel diameter which might affect the incidence of PMI. A variable with two tailed p-value <0.05 was considered as statistically significant.

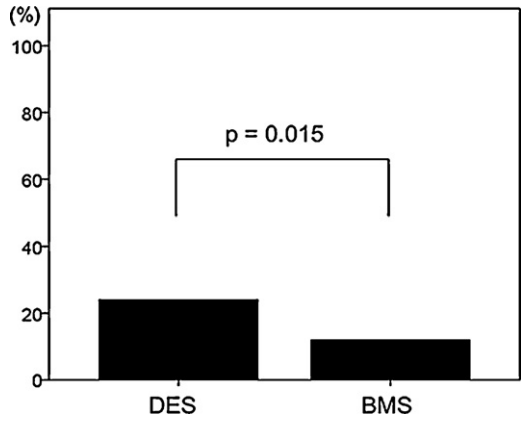

Fig. 1. Incidence of periprocedural myocardial injury (PMI). In patients treated with drug-eluting stents (DESs) the incidence of PMI was 24%, against 12% in patients treated with bare-metal stent (BMS) ($p=0.015$, chi-square test), when PMI was defined as an increase in creatine kinase-myocardial band isozyme fraction greater than the upper limit of the reference range.

Results

Patients were divided into two groups (DES group, $n=136$ and BMS group, $n=129$). Table 1 shows the clinical characteristics of both groups. Body mass index was significantly higher in the DES group than in the BMS group (24.3 ± 3.6 kg/m^2 vs. 23.1 ± 3.8 kg/m^2, $p=0.012$). The rate of multi-vessel disease was significantly higher in the DES group than the BMS group (49% vs. 25%, $p<0.001$). Significantly higher CK-MB levels 24 h after PCI were obtained in the DES group compared to the BMS group (21.0 ± 23.6 IU/l vs. 15.4 ± 21.8 IU/l, $p=0.045$). The incidence of PMI was significantly higher in the DES group than in the BMS group (24% vs. 12%, $p=0.015$) (Fig. 1). However, when PMI was defined as an increase in CK-MB three times greater than the ULN, the statistical significance disappeared [3 (2%) vs. 1 (1%), $p=0.623$]. Furthermore, no patients experienced PMI, when it was defined as an increase in CK-MB five times greater than the ULN (Table 2). Low-density lipoprotein cholesterol levels were significantly lower in the DES group than the BMS group (99.0 ± 27.6 mg/dl vs. 107.7 ± 34.0 mg/dl, $p=0.023$). Patients in the DES group significantly more frequently took angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) (65% vs. 51%, $p=0.017$) than those in the BMS group. Table 3 provides the data for angiograms and PCI procedure. DES were more frequently implanted in the left circumflex artery and less frequently implanted in the right coronary artery than BMS (32% vs. 12%, $p<0.001$ and 24% vs. 41%, $p<0.001$). In addition, DESs were more frequently used to treat complex lesions than BMS (54% vs. 31%, $p<0.001$). In the DES group, patients had significantly smaller vessels and had longer lesions than those in the BMS group (2.5 ± 0.61 mm vs. 2.7 ± 0.58 mm, $p=0.036$ and 16.2 ± 4.6 mm vs. 11.5 ± 3.7 mm, $p<0.001$). As to PCI procedure, a significantly larger number of stents was implanted (1.3 ± 0.49 vs. 1.2 ± 0.40, $p=0.010$) and smaller size with longer stent were used in the DES group than in the BMS group (2.8 ± 0.30 mm vs. 3.3 ± 0.45 mm, $p<0.001$ and 23.8 ± 12.4 mm vs. 15.9 ± 6.0 mm, $p<0.001$). Total balloon inflation time was significantly longer

Table 3
Data on angiograms, QCA, and PCI procedure.

	All $n=265$	DES $n=136$	BMS $n=129$	p
Culprit lesion location				
Left anterior descending artery	121 (46)	61 (45)	60 (47)	0.806
Left circumflex artery	59 (22)	43 (32)	16 (12)	<0.001
Right coronary artery	85 (32)	32 (24)	53 (41)	<0.001
Complex lesion (type B2/C[a])	114 (43)	74 (54)	40 (31)	<0.001
QCA pre-procedure				
Minimum lumen diameter (mm)	0.68 ± 0.37	0.66 ± 0.33	0.71 ± 0.42	0.232
Reference vessel diameter (mm)	2.6 ± 0.59	2.5 ± 0.61	2.7 ± 0.58	0.036
Diameter stenosis (%)	73 ± 13	72 ± 12	74 ± 13	0.260
Lesion length (mm)	13.9 ± 4.8	16.2 ± 4.6	11.5 ± 3.7	<0.001
QCA post-procedure				
Minimum lumen diameter (mm)	2.6 ± 0.50	2.5 ± 0.42	2.8 ± 0.51	<0.001
Reference vessel diameter (mm)	2.9 ± 0.51	2.8 ± 0.45	3.1 ± 0.50	<0.001
Diameter stenosis (%)	10.2 ± 6.6	11 ± 6	10 ± 7	0.112
Lesion length (mm)	18.1 ± 6.7	21.2 ± 6.1	14.8 ± 5.6	<0.001
PCI procedure				
Direct stenting	31 (12)	16 (12)	15 (12)	1.000
Number of stents	1.3 ± 0.46	1.3 ± 0.49	1.2 ± 0.40	0.010
Stent size (φ, mm)	3.0 ± 0.45	2.8 ± 0.30	3.3 ± 0.45	<0.001
Total stent length (mm)	20.0 ± 10.5	23.8 ± 12.4	15.9 ± 6.0	<0.001
Maximum inflation pressure (atm)	15.1 ± 3.5	15.5 ± 3.7	14.8 ± 3.3	0.129
Total balloon inflation time (s)	119.2 ± 22.5	126.7 ± 24.5	111.4 ± 17.2	<0.001

Values are mean ± SD or number (%).

[a] Lesion type was classified according to American Heart Association/American College of Cardiology definition; DES, drug-eluting stent; BMS, bare-metal stent; QCA, quantitative coronary angiography; PCI, percutaneous coronary intervention.

Table 4
Univariate and multivariate logistic regression analyses for periprocedural myocardial injury.

Variable	Univariate			Multivariate		
	Odds ratio	95% Confidence interval	*p*	Odds ratio	95% Confidence interval	*p*
Age	0.99	0.97–1.02	0.547			
Male	0.65	0.33–1.25	0.195	0.69	0.34–1.43	0.320
Body mass index	1.04	0.96–1.12	0.318			
Hypertension	0.85	0.44–1.64	0.630		0.78–2.61	0.256
Diabetes	0.84	0.48–1.45	0.531		1.00–1.02	0.045
Current smoker	0.98	0.53–1.82	0.954			
Multiple vessel disease	1.69	0.97–2.96	0.065	1.42	0.40–1.25	0.231
LDL-C	1.01	1.00–1.02	0.159	1.01		
HDL-C	1.01	0.99–1.03	0.532		0.84–2.87	0.162
Hemoglobin A1c	0.91	0.70–1.20	0.517		0.56–1.60	0.843
High sensitivity					0.90–1.04	0.344
C-reactive protein	0.89	0.66–1.20	0.430			
ACE-I and/or ARB	1.00	0.57–1.74	0.997		0.39–2.14	0.833
Calcium channel blockers	0.65	0.38–1.13	0.128	0.70	0.97–1.03	0.893
Beta-blockers	1.09	0.58–2.02	0.797			
Nitrates	1.44	0.75–2.78	0.273		1.09–5.70	0.031
Complex lesion (type B2/C[a])	1.81	1.04–3.15	0.036	1.55		
Reference vessel diameter	0.89	0.56–1.40	0.604	0.95		
Lesion length	1.02	0.96–1.07	0.608	0.97		
Direct stenting	1.66	0.75–3.67	0.211			
Number of stent	1.23	0.68–2.21	0.501			
Stent size	0.51	0.27–0.98	0.044	0.91		
Total stent length	1.02	0.99–1.04	0.150	1.00		
Maximum inflation pressure	1.02	0.95–1.12	0.546			
Total balloon inflation time	1.00	0.99–1.01	0.817			
DES use	2.38	1.34–4.23	0.003	2.49		

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; DES, drug-eluting stent.

[a] Lesion type was classified according to American Heart Association/American College of Cardiology definition.

in the DES group than in the BMS group (126.7 ± 24.5 s vs. 111.4 ± 17.2 s, $p < 0.001$). No death, myocardial infarction, or repeat revascularization was seen in enrolled patients during their hospitalization. Using multivariate logistic regression analysis after adjustment for the confounding factors, low-density lipoprotein cholesterol levels and use of DES remained independent predictors for PMI (odds ratio 1.01, 95% CI 1.00–1.02, $p = 0.045$, and odds ratio 2.49, 95% CI 1.09–5.70, $p = 0.031$, respectively) (Table 4). In our subanalysis, among patients treated with DES, sirolimus-eluting stents were implanted in 69 (51%) patients and paclitaxel-eluting stents in 67 (49%). No significant difference was seen in the incidence of PMI between the use of a sirolimus- and a paclitaxel-eluting stent (28% vs. 19%, $p = 0.314$).

Discussion

A major finding of this non-randomized study was that sirolimus- and paclitaxel-eluting stent implantation significantly increased the incidence of PMI after successful PCI compared to BMS implantation. Recently, DES implantation has been one of the standard treatments for AP patients. Use of a DES remarkably reduces the incidence of restenosis and the need for repeat revascularization compared to that of BMS [3–5]. Restenosis after PCI is reportedly associated with increased risk of death [2]. Thus, preventing restenosis may improve the clinical outcome including a lower mortality rate. However, until now, use of DES has not improved mortality in patients with AP in spite of their notable suppressive effect for neointimal hyperplasia compared to that of BMS [6–8]. Several mechanisms may explain this discrepancy. Although stent thrombosis which likely occurs after DES implantation is a reasonable explanation [17–20], this matter has not been fully elucidated. In such situations, we hypothesized that DES implantation may be associated with a higher incidence of PMI and affect the clinical outcome after PCI. PMI diagnosed by elevation in plasma levels of cardiac enzyme, such as CK-MB and cardiac troponin even after successful PCI is a predictor of poor prognosis [9–12]. Ioannidis et al. have demonstrated that CK-MB ratio 1–3, 3–5, and >5, carried a relative risk of mortality; 1.5, 1.8, and 3.1, respectively [11]. Akkerhuis et al. also reported that in patients with CK-MB ratios of 0–1, 1–3, 3–5, 5–10, and >10, the risk of death was 1.3, 2.0, 2.3, 4.3, and 7.4%, respectively [12]. Therefore, our results might be one possible reason why DES cannot improve the mortality of patients despite their evident risk reduction of restenosis compared to BMS.

The causes of PMI are multifactorial and include patient, angiographic, and procedural factors [21]. Of these procedural factors are important [22]. More complex lesions require a more complex procedure to predispose to PMI [21]. In the present study, patients treated with DES had worse metabolic profiles, more complex lesions, and were treated with more complicated procedures than those treated with BMS. However, even after adjustment for these confounding factors, DES implantation remained an independent predictor for PMI. Side branch occlusion and distal embolization are considered as important causes of PMI. However, in this study, we excluded patients with major branch occlusion or slow-flow/no-reflow phenomenon. Microcirculatory plugging of platelets and neutrophils caused by platelet activation, thrombosis, and inflammation might be associated with PMI [23]. Therefore, microcirculatory injury due to minor side branch occlusion and/or distal embolization which could not be detected by angiography might be a possible mechanism of PMI. Microcirculatory vasospasm introduced by exposure to vasoconstrictors is also considered as a possible cause of PMI [23]. In vitro experiments have suggested that the first generation DES may decrease NO bioavailability, resulting in impaired endothelial-dependent vasorelaxation [24,25]. In a clinical setting, impaired endothelial-dependent vasomotor function which is detected by paradoxical vasoconstriction via stimuli of acetylcholine infusion, after the first-generation DES implantation is well documented [22–32]. In such a situation, it could be speculated that microcirculatory vasospasm via hypersensitivity reaction from the polymer and/or drug, as well as direct toxic effect from

the released drug might be possible mechanisms of our findings. However, this theory is just speculation, thus, further investigations providing insight into the potential mechanism of our results are warranted.

In the present study, to detect PMI perceptively, we defined PMI as an increase in CK-MB greater than the ULN. However, when we applied the definitions of it as an increase in CK-MB three or five times greater than the ULN, the association of high incidence of PMI with DES use disappeared. In our institution, both statins and thienopyridine drugs are prescribed to all patients undergoing elective PCI to prevent PMI, if not contraindicated [33–36]. In addition to the relatively small sample size of this study, these might be reasons for aforementioned discrepancies and differences between our results and those of previous studies [3,4]. Furthermore, this study was a non-randomized study. Therefore, there was likely selection bias since DES might be used in patients who were generally considered as high-risk subjects for restenosis. Although multivariate analysis demonstrated that use of DES was an independent predictor for PMI, we could not completely adjust all potential factors affecting PMI. For these reasons, our findings should be interpreted carefully. In addition, this study consisted of patients treated with many types of coronary stents with various designs, limiting the generalization of our results.

In conclusion, our results demonstrated that the first-generation DES implantation was associated with a higher prevalence of PMI in stable AP patients compared to BMS implantation, when we defined PMI as an increase in CK-MB greater than the ULN after the procedure. Although this relationship depended on the definitions for PMI, they might be a possible reason why DES could not improve long-term mortality despite their promising effect for the prevention of restenosis. To confirm our speculations, clinical outcomes including cardiovascular events must be collected in long-term follow-up.

Disclosures

None to declare.

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